IN THE DRAWINGS

Replacement figures 1-3 are being submitted.

REMARKS

Consideration of the patent application, as preliminarily amended, is respectfully requested.

By this amendment of the specification, the applicant has corrected various typographical errors which he has found, filled in the blank spaces in the text of the specification with now issued U.S. Application Nos., and described his invention with more precision.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning at page 2, line 14 has been amended as follows:

The motion of bodies are determined by Newton's Laws of Motion. For a body subject to a force, Newton's Second Law:

$$F = ma$$

or the acceleration of the body of mass is [equal] proportional to the total force upon the body is applicable. This simple equation hides enormous complexity for the dynamic modeling and static analysis of large molecules. The acceleration of the body is the time derivative of velocity of the body and to determine the velocity of the body, its acceleration must be integrated with respect to time. Likewise, the velocity of a body is the time derivative of position of the body and to determine the position of the body, its velocity must be integrated with respect to time. Thus with knowledge of the force upon a body, integration operations must be performed to determine the velocity and position of the body at a given time.

The paragraph beginning at page 4, line 10 has been amended as follows:

Attempts have been made to apply residual (or error) functions rather than direct computation of state derivatives to the integration problem when using implicit integration methods. These attempts did not lead to any practical success, in large part because the mechanical systems to which the methods were applied were highly cyclic in nature (cyclic meaning many closed loops in the system topology). This necessitated the introduction of additional algebraic quantities into the system description and this

complication led to poor conditioning of the equation which caused failure of a certain numerical step central to implicit integrators.

The paragraph beginning at page 4, line 10 has been amended as follows:

However, molecular models are almost entirely acyclic (very few or no loops in the system topology), and the additional algebraic variables do not need to be introduced into the system model. In the present invention the Residual Form is able to provide a significant speedup to a portion of the computation with a much simpler formulation of the molecular model and its equations of motion. It is believed that Residual Form has never been used in conjunction with molecular modeling and in particular, MD simulations, primarily because MD simulations are usually devised to use explicit numerical methods to advance the molecular model through time, whereas the Residual Form requires the use of implicit numerical methods (see co-pending U.S. Application No. 10/053,253, entitled "METHOD FOR LARGE TIMESTEPS IN MOLECULAR MODELING" and filed on even date, which claims priority from the previously referenced provisional patent applications, and which co-pending application is incorporated by reference in its entirety).

The paragraph beginning at page 8, line 6 has been amended as follows:

The general system architecture 48 of the software and some of its processes for modeling molecules in accordance with the present invention are illustrated in Fig. 1. Each large rectangular block represents a software module and arrows represents information which passes between the software modules. The software system architecture has a modeler module 50, a [biochem] biochemistry components module 52, a physical model module 54, an analysis module 56 and a visualization module 58. The details of some of these modules are described below; other modules are available to the public.

The paragraph beginning at page 8, line 13 has been amended as follows:

The modeler module 50 provides an interface for the user to enter the physical parameters which define a particular molecular system. The interface may have a graphical or data file input (or both). The [biochem] biochemistry components module 52 translates the modeler input for a particular mathematical model of the molecular system and is divided into translation submodules 60, 62 and 64 for mathematical modeling the molecule(s), the force fields and the solvent respectively of the system being modeled. There are several modeler and [biochem] biochemistry components modules available including, for example, Tinker (Jay Ponder, TINKER User's Guide, Version 3.8, October 2000, Washington University, St. Louis, MO).

The paragraph beginning at page 8, line 21 has been amended as follows:

With the translated physical parameters from the [biochem] biochemistry components module 52, the physical model module 54 defines the molecular system mathematically. At the core of the module 54 is a multibody system submodule 66. The physical model module 54 and multibody system submodule 66 are described below in detail. Co-pending application, U.S. Appln. No. 10/053/348, entitled, "METHOD FOR ANALYTICAL JACOBIAN COMPUTATION IN MOLECULAR MODELING," and filed on even date, which claims priority from the previously referenced provisional patent applications and which co-pending application is incorporated by reference in its entirety, has further descriptions of the physical model module 54 and multibody submodule 66.

The paragraph beginning at page 9, line 6 has been amended as follows:

The visualization module 58 receives input information from the [biochem] biochemistry components module 52 and the analysis module 56 to provide

the user with a three-dimensional graphical representation of the molecular system and the solutions obtained for the molecular system. Many visualization modules are presently available, an example being VMD (A. Dalke, *et al.*, VMD User's Guide, Version 1.5, June 2000, Theoretical Biophysics Group, University of Illinois, Urbana, Illinois).

The paragraph beginning at page 9, line 24 has been amended as follows:

The MBS is an abstraction of the atoms and effectively rigid bonds that make up the molecular system being modeled and is selected to simplify the actual physical system, the molecule in its environment, without losing the features important to the problem being addressed by the simulation. With respect to the general system architecture illustrated in Fig. 1, the MBS does not include the electrostatic charge or other energetic interactions between atoms nor the model of the solvent in which the molecules are immersed. The force fields are modeled in the submodule 62 and the solvent in the submodule 64 in the [biochem] biochemistry components module 52.

The paragraph beginning at page 12, line 28 has been amended as follows:

Given the generalized coordinates for a particular joint, two quantities: $r^{P_k Q_k}(k)$, the joint translation vector, and ${}^{i}C^{k}(k)$, the direction cosine matrix for body k in its parent frame, are formed. The translation vector $r^{P_k Q_k}(k)$ expresses the vector from the inboard hinge point P of body k to the hinge point Q of body k, in the coordinate frame of the parent body. Details of these computations depend on the joint type and can be easily derived. For purposes of this description, access to a function that can generate $r^{P_k Q_k}(k)$ and ${}^{i}C^{k}(k)$ given the system generalized coordinates is assumed.

The paragraph beginning at page 21, line 2 has been amended as follows:

Hence the present invention improves the speed with which accurate molecular dynamics simulations can be performed. The method allows a numerical integration algorithm to utilize a representation of the differential equations that requires fewer arithmetic operations to evaluate than previous methods. The Residual Form method of the equations includes $0 = M\dot{u} - f$ whereas the Direct Form method includes $\dot{u} = M^{-1} f$. The Direct Form method requires evaluation of the state derivatives, and while this can be done efficiently using Order(N) methods, the Residual Form can be computed with less cost. In addition, an analytical Jacobian of the residual equations can be formed at less cost than the analytical Jacobian of the direct equations (see previously referenced co-pending application, U.S. Appln. No. 10/053,348, entitled, "METHOD FOR ANALYTICAL JACOBIAN COMPUTATION IN MOLECULAR MODELING," and filed on even date. A Jacobian is required by stable implicit integration methods and its formation is often the most time-consuming step in such methods.

The paragraph beginning at page 21, line 25 has been amended as follows:

Therefore, while the foregoing is a complete description of some of the embodiments of the invention, it should be evident that various modifications, alternatives and equivalents may be made and used. Accordingly, the above description should not be taken as limiting the scope of the invention which is defined by the metes and bounds of the appended claims.